JACC Vol. 12, No. 3
September 1988:773–80

REPORTS ON THERAPY

Use of an Ultrashort-Acting Beta-Receptor Blocker (Esmolol) in Patients With Acute Myocardial Ischemia and Relative Contraindications to Beta-Blockade Therapy

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The hemodynamic responses to esmolol, an ultrashort-acting ($t_{1/2}$ = 9 min) beta$_1$-adrenergic receptor antagonist, were examined in 16 patients with myocardial ischemia and compromised left ventricular function as evidenced by a mean pulmonary capillary wedge pressure of 15 to 25 mm Hg. Esmolol was infused intravenously to a maximal dose of 300 μg/kg body weight per min for ≤48 h in 16 patients: 9 with acute myocardial infarction, 6 with perinfarction angina and 1 with acute unstable angina. The sinus rate and systolic arterial pressure declined rapidly in all patients from baseline values of 99 ± 12 beats/min and 126 ± 19 mm Hg to 80 ± 14 beats/min ($p < 0.05$) and 107 ± 20 mm Hg ($p \leq 0.05$) during esmolol treatment. Rate-pressure product decreased by 33% and cardiac index by 14% during esmolol treatment, but pulmonary capillary wedge pressure was not significantly altered by drug infusion (19 ± 3 mm Hg at baseline versus 19 ± 5 during treatment, p = NS). In all patients there was a rapid return toward baseline hemodynamic measurements within 15 min of stopping administration of esmolol, and virtually complete resolution of drug effect was evident within approximately 30 min.

During infusion of esmolol, four of nine patients receiving intravenous nitroglycerin required downward adjustment of nitroglycerin infusion rate to maintain systolic blood pressure >90 mm Hg. Four patients required termination of esmolol infusion because of oliguria or hypotension, but all recovered hemodynamic stability within 30 min of termination of the infusion; one patient required a brief infusion of dopamine.

These results suggest that, even in the presence of moderate left ventricular dysfunction, esmolol safely and effectively lowers both arterial pressure and heart rate in patients with acute ischemia. The titratability and rapid offset of action of esmolol in such patients may broaden the clinical applicability of the adjunctive cardioprotective effect of beta-receptor blockade in the current era of reperfusion therapy for myocardial infarction.

(J Am Coll Cardiol 1988;12:773–80)

Many clinical and experimental studies (1,2) have demonstrated that beta-adrenoceptor blocking agents are beneficial during myocardial ischemia. The use of beta-blockers soon after the onset of chest pain in patients with suspected acute myocardial infarction or unstable angina is effective in reducing the risk of progression to infarction or reinfarction (3,4); usage is effective as well in reducing the incidence of ventricular fibrillation and total cardiac mortality during the initial phase of hospitalization for myocardial infarction (5,6). Review of beta-blockade trials in myocardial infarction (7,8) also suggests that early treatment may reduce infarct size by 15 to 20%.

In carefully screened patients with acute ischemia, the risk of initiating or exacerbating congestive heart failure, hypotension, bradycardia, heart block or bronchospasm with intravenous beta-blockers is generally <5% (9–11). Nonetheless, practicing clinicians remain concerned about precipitating such adverse reactions and this often precludes the use of beta-blockers in patients who may be among those

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Manuscript received January 4, 1988; revised manuscript received March 20, 1988, accepted April 7, 1988.

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0735-1097/88/$3.50

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most likely to benefit from such therapy (12). In recent randomized clinical trials (13–15), nearly a quarter of patients with early infarction initially screened for enrollment were excluded from participation because of the presence of an absolute or relative contraindication to beta-blockade.

Esmolol, a recently released ultrashort-acting cardioselective beta-blocker, may prove useful in this setting because its short biologic half-life ($t_{1/2\beta}$ = 9 min) would allow both rapid titration to a specific hemodynamic target and rapid reversal of drug effect should any untoward reaction occur (16). Esmolol has been used in clinical studies (17–23) that have confirmed its safety and efficacy in the treatment of supraventricular arrhythmias and in the management of tachycardia or hypertension associated with anesthesia induction, tracheal intubation or the postoperative period. In animal studies, esmolol appeared to reduce ischemic myocardial damage (24); it was effective in lowering the heart rate and blood pressure in patients with myocardial infarction or unstable angina (25). The clinical use of a titratable beta-blocker would broaden the potential application of intravenous beta-blockade in the setting of acute ischemic heart disease to include patients with relative contraindications to beta-blockade therapy.

Therefore, the purpose of this investigation was twofold: 1) to study the pharmacodynamic profile of esmolol in patients with acute ischemia and compromised left ventricular function, and 2) to assess the safety of acute intravenous beta-blockade with an ultrashort-acting agent in patients with a relative contraindication to beta-blocker treatment.

Methods

Study patients. We previously reported (25) the hemodynamic effects of short-term use of esmolol in 19 patients with acute myocardial ischemia. Esmolol produced an easily titratable reduction in heart rate, blood pressure and cardiac output without any appreciable effect on pulmonary capillary wedge pressure or PR interval. To determine if patients with relative hemodynamic contraindications to beta-blockade had a less favorable response to esmolol, we studied an additional 10 patients with acute myocardial infarction or unstable angina associated with compromised left ventricular function as evidenced by an elevated mean pulmonary capillary wedge pressure. The present report details the hemodynamic response in these 10 patients plus a subset of 6 patients from our prior report (25) who had similar degrees of compromised left ventricular function.

Sixteen patients (6 men and 10 women), aged 65 ± 11 (mean ± SD) years, with a mean pulmonary capillary wedge pressure of 15 to 25 mm Hg and thus considered to have a relative contraindication to beta-blockade were enrolled. All patients had active ischemic heart disease. Nine patients without ongoing active ischemia were studied between 4 and 24 h after onset of acute myocardial infarction; six were treated because of angina at rest occurring >24 h but <1 week after myocardial infarction, and one received therapy for acute unstable angina without evidence for recent infarction. All patients had sinus rhythm with a ventricular rate >75 beats/min before the esmolol infusion, which was carried out in the coronary care unit of Brigham and Women's Hospital.

Acute myocardial infarction was diagnosed by a history of typical chest pain lasting ≥30 min, an increase in total serum creatine kinase (CK) above the normal range associated with the presence of the myocardial-specific isoenzyme MB CK at twice the normal range and evolutionary ST-T wave and QRS criteria for myocardial infarction including R wave loss and development of pathologic Q waves. Unstable angina was characterized by ischemic chest pain occurring at rest, accompanied by transient electrocardiographic (ECG) changes of ST segment elevation or depression or T wave flattening or inversion. Any such episodes in which ECG changes and ischemic pain occurred in the absence of serum CK elevation >24 h after acute infarction were also considered indications of unstable angina.

Patients were excluded if they had systolic blood pressure <110 mm Hg before therapy, second or third degree atrioventricular (AV) block, new bilateral bundle branch block or trifascicular block, a prior history of bronchospasm or severe chronic obstructive pulmonary disease, cardiogenic shock or pulmonary capillary wedge pressure >25 mm Hg, severely impaired renal or hepatic function or significant cardiac valvular disease or treatment with a beta-blocker within ≥2 excretory half-lives before trial entry. All patients who participated gave written informed consent, and the study protocol was approved by the Human Subjects Committee of the Brigham and Women's Hospital. After consent was obtained, a 24 h ECG monitor was applied and baseline hemodynamics were determined immediately before initiation of the esmolol infusion.

Treatment protocol. Pulmonary artery balloon flotation catheters were inserted in all 16 patients. A 10 mg/ml solution of esmolol (Brevibloc, Dupont Critical Care) was infused with an IMED model 927 volumetric pump into a peripheral vein in each patient. The drug was administered over a 35 min titration period consisting of up to seven consecutive 5 min infusion periods. Each infusion period consisted of a 500 μg/kg body weight per min loading dose for 30 s followed by a 4.5 min infusion of 25, then 50 μg/kg per min of esmolol. The loading dose was then increased to 500 μg/kg per min for 1 min followed by 4 min infusions of 100, 150, 200, 250 and 300 μg/kg per min of esmolol. This regimen was followed until either the peak dose of 300 μg/kg per min had been given, the rate-pressure product decreased by >30% or systolic pressure decreased to <90 mm Hg or if bronchospasm, cardiogenic shock, heart rate <60 beats/min or second degree or greater heart block developed. If nec-

essary, the dose of esmolol was decreased to restore the systolic arterial pressure to >90 mm Hg.

The maximal rate of infusion that each patient tolerated was continued during a maintenance period that lasted up to an additional 48 h after which the infusion was stopped. Patients were monitored for ≥30 min after termination of the infusion. Heart rate was determined from the ECG after each 5 min titration period, hourly during the maintenance phase and every 5 min during the 30 min follow-up period. Blood pressure (measured by the cuff occlusion method), pulmonary artery pressure and the mean pressure in the pulmonary capillary wedge position were similarly monitored. Cardiac index was determined at baseline, after the titration period, at the end of the maintenance period and 30 min after termination of the infusion by the thermodilution method with an Instrumentation Laboratories model 701 cardiac output computer (mean of 3 to 5 measurements).

The design of this study did not include monitoring of ST segments for evidence of silent ischemia but rather focused on symptomatic episodes of ischemia for which ECGs were obtained as clinically indicated. All patients were continuously monitored for evidence of cardiac arrhythmias by way of hardwire ECG bedside monitors. Physical examination and standard laboratory tests (urinalysis, complete blood count and chemistry values) were performed before and after the esmolol infusion.

Mean arterial pressure (mm Hg) was calculated as (2 × diastolic + systolic pressure)/3, and the rate-pressure product was defined as systolic blood pressure × heart rate.

Statistical analysis. Data were analyzed by a repeated measures analysis of variance. Results are presented as mean values ± 1 SD and differences were considered statistically significant at the $p \leq 0.05$ level.

Results

Effects of esmolol on heart rate, blood pressure and rate-pressure product (Table 1). Esmolol rapidly produced a significant reduction in sinus rate without the development of clinically significant prolongation of AV conduction in any patient (the PR interval was 0.17 ± 0.03 s at baseline and was 0.17 ± 0.03 s at the end of the maintenance infusion, p = NS). The mean baseline sinus rate of 99 ± 12 beats/min (range 79 to 118) decreased to 87 ± 13 beats/min within 10 min of starting the infusion at a dose of 50 μg/kg per min and to a nadir of 80 ± 14 beats/min ($p \leq 0.05$ versus baseline) during the maintenance phase (Fig. 1). Further augmentation of the esmolol infusion resulted in only a modest additional reduction in sinus rate with most patients achieving the maximal decrease in sinus rate at a dose of 100 to 200 μg/kg per min. There was no significant change in the sinus rate during the maintenance phase. Within 15 min of stopping the infusion there was a rapid increase in sinus rate and virtually complete resolution of drug effect occurred within approximately 30 min.

Table 1. Summary of Hemodynamic and Electrical Responses to Esmolol in 16 Patients With Acute Myocardial Ischemia

	Baseline	End Maintenance	Recovery (30 min after esmolol)
Heart rate (beats/min)	99 ± 12	80 ± 14*	92 ± 17†‡
Blood pressure (mm Hg)			
Systolic	126 ± 19	107 ± 20*	124 ± 22†‡
Diastolic	71 ± 12	62 ± 8*	69 ± 9†
Rate-pressure product ($\times 10^3$)	12.5 ± 2.7	8.4 ± 1.9*	11.5 ± 3.4*‡
PCW (mm Hg)	19 ± 3	19 ± 5	17 ± 5‡
Cardiac index (liters/min per m²)	2.9 ± 0.7	2.5 ± 0.8	2.8 ± 0.7‡
PR interval (s)	0.17	0.17	0.17‡

*$p < 0.05$ vs. baseline; †$p < 0.05$ vs. maintenance; ‡p = NS vs. baseline.
PCW = mean pulmonary capillary wedge pressure.

The systemic arterial pressure responded similarly with a decline from 126 ± 19/71 ± 12 [89 ± 11] mm Hg (systolic/diastolic [mean]) at baseline to 107 ± 20/62 ± 8 [78 ± 10] mm Hg at the end of the maintenance phase. As compared with baseline values these results represented a 15% decrease in systolic, 13% decrease in diastolic and a 12% decrease in mean pressures. There was no significant change in blood pressure during the maintenance phase, and within 30 min after termination of the infusion the arterial pressure returned to 124 ± 22/69 ± 9 [87 ± 10] mm Hg (p = NS versus baseline) (Fig. 2). Unlike the heart rate response, there appeared to be a persistent dose-dependent effect of esmolol on arterial pressure with a continuing decline in pressure as the dose was increased.

The decline in arterial pressure and heart rate resulted in a decline in rate-pressure product of 33% by the end of the maintenance phase achieved at a mean dose of 172 ± 80 μg/kg per min. Thirty minutes after the esmolol infusion was stopped the mean rate-pressure product returned to ≤9% of the baseline values.

Effects of esmolol on pulmonary capillary wedge and cardiac index (Table 1). Pulmonary capillary wedge pressure was not significantly altered during the esmolol infusion (19 ± 3 mm Hg [baseline] versus 19 ± 5 mm Hg [end-maintenance], p = NS), whereas the cardiac index declined approximately 14% (2.9 ± 0.7 to 2.5 ± 0.8, p = NS) by the end of the maintenance period and no clinical congestive heart failure occurred (Fig. 3). Even in patients who required early termination of the esmolol infusion because of oliguria or hypotension (see next paragraph), there was no significant change in pulmonary capillary wedge pressure.

Adverse reactions during esmolol infusion. Nine of the 16 patients were additionally receiving intravenous nitroglycerin at the start of the esmolol infusion and 4 required

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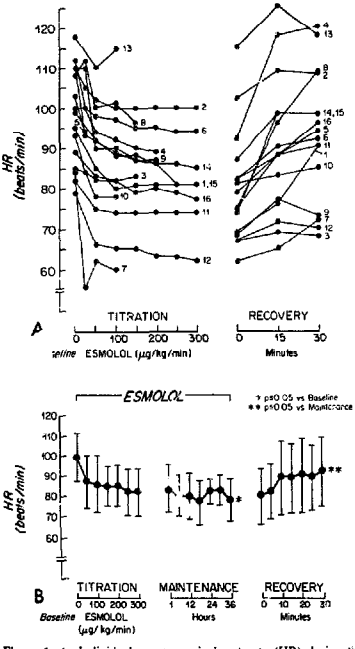

Figure 1. A, Individual responses in heart rate (HR) during the titration and recovery phases of esmolol infusion. B, Mean heart rate (±SD) in all 16 patients during the titration, maintenance and recovery phases. Recovery values for Patient 16 are not included because this patient required a short-term dopamine infusion during data collection in the recovery phase.

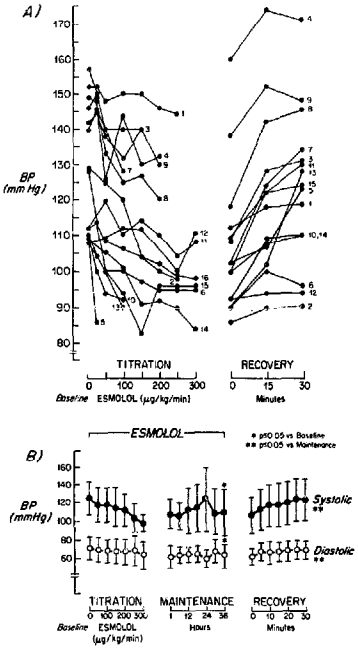

Figure 2. A, Individual responses in systolic blood pressure (BP) during the titration and recovery phases of the esmolol infusion. B, Systolic and diastolic (mean ± SD) arterial pressure in all 16 patients during the titration, maintenance and recovery phases. Recovery values for Patient 16 are not included because this patient required a short dopamine infusion during data collection in the recovery phase.

titration downward of the nitroglycerin infusion rate to prevent a decline in arterial pressure <90 mm Hg systolic. One of these four patients developed recurrent angina that required resumption of intravenous nitroglycerin and subsequent discontinuation of esmolol to maintain the systolic pressure >90 mm Hg. None of the other patients who underwent downward titration of nitroglycerin infusion developed clinical ischemic symptoms.

Two patients, both receiving intravenous nitroglycerin, underwent downward titration of the esmolol maintenance infusion rate (from 300 to 200 and from 300 to 150 μg/kg per min, respectively) because they had a reduction in systolic arterial pressure to <90 mm Hg although they were asymptomatic. In both patients a reduction in the infusion rate resulted in a return of systolic pressure to >90 mm Hg.

Four patients, one of whom was receiving intravenous nitroglycerin at 200 to 500 μg/min, required termination of the esmolol infusion because of either oliguria (one patient) or continued systolic hypotension (three patients) (Fig. 4). The first patient was an 82 year old man with persistent angina at rest after a non-Q wave myocardial infarction. His

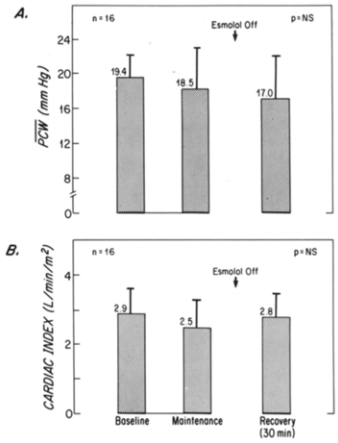

Figure 3. A, Mean pulmonary capillary wedge pressure (PCW) and B, cardiac index in all 16 patients at baseline, end of maintenance infusion and 30 min after termination of esmolol infusion.

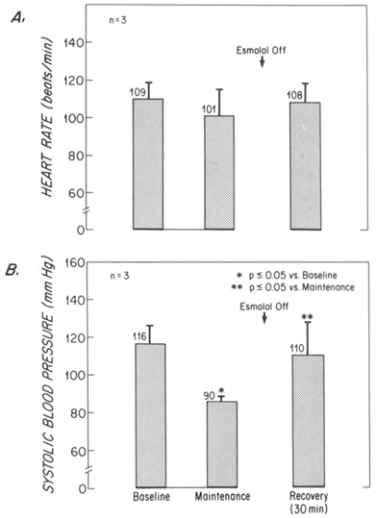

Figure 4. A, Heart rate response in three patients with compromised left ventricular function and a hypotensive or oliguric reaction. The heart rate returned to baseline values in all three patients within 30 min of termination of esmolol infusion. B, Systolic arterial pressure response in the same three patients. Blood pressure returned toward baseline values within 30 min after termination of the infusion. One patient (data not shown) required a brief infusion of dopamine to reestablish baseline arterial pressure.

heart rate at rest and blood pressure declined from 103 beats/min and 158/81 mm Hg to a nadir of 69 beats/min and 112/72 mm Hg after a 5 h infusion of esmolol. This result was associated with a >50% decrease in rate-pressure product, a decline in cardiac index from 2.5 to 1.5 liters/min per m^2 and no change in pulmonary capillary wedge pressure. Because urine output declined to <10 ml/h, the esmolol infusion was discontinued. Thirty minutes later the heart rate was 90 beats/min, blood pressure 118/74 mm Hg and urine output returned to >30 to 50 ml/h. The other three patients all received esmolol within 24 h of an acute infarction and transient hypotension developed as a direct drug effect in one, during an acute vagal episode in the second and during a recurrent ischemic episode in the third. Discontinuation of esmolol administration resolved the hypotension in the first two patients, whereas a brief infusion of dopamine was necessary in the third, whose blood pressure recovered within 20 min of discontinuation of esmolol infusion. The time course for recovery of heart rate and arterial pressure in these three patients is depicted in Figure 4.

Despite the relative contraindications to beta-blockers in the patients studied, there were no episodes of initiation or exacerbation of overt congestive heart failure or clinically symptomatic hypotension or bradycardia. Routine blood, urinary and ECG studies showed no significant alteration during the infusion. As mentioned previously, drug-induced declines in systolic pressure rapidly and reliably resolved after termination of the esmolol infusion when the systolic blood pressure decreased to <90 mm Hg.

Discussion

Rationale for beta-blockade in myocardial ischemia. Beta-adrenoceptor blocking agents are frequently used in the contemporary management of patients with an acute ischemic syndrome because they reduce myocardial oxygen demand by lowering heart rate, arterial pressure and myocardial contractility. Several studies (26) have demonstrated their efficacy in diminishing the frequency of angina, raising the anginal threshold, aborting threatened myocardial infarction and reducing mortality or the incidence of reinfarction in

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patients surviving myocardial infarction. Clinical studies assessing the ability of beta-blockers to limit myocardial infarct size suggest that at least a moderate reduction in cumulative myocardial-specific enzyme release occurs when the drug is administered soon after the onset of chest pain.

Pooled results from many trials (6) employing early intravenous beta-blockade for acute myocardial infarction persistently demonstrate an approximately 15% reduction in mortality, ventricular fibrillation and reinfarction during the 1st week after infarction. The two largest trials to date, International Study of Infarct Survival (ISIS-1) (atenolol) (6) and Metoprolol in Acute Myocardial Infarction (MIAMI) (metoprolol) (27) suggest that the reduced mortality benefit occurs primarily within the 1st day after myocardial infarction. Thus, to achieve this improvement in initial postinfarction survival, early intervention appears necessary.

Risks of beta-blockade in myocardial ischemia. The risks associated with immediate use of beta-blockers in patients with myocardial infarction are not firmly established. In three recent large scale clinical trials (13–15) of beta-blockade therapy after myocardial infarction, 47 to 77% of patients initially screened were not enrolled because of administrative considerations, continued use of beta-blockers or refusal to participate, and 18 to 28% of otherwise eligible patients were specifically excluded because of absolute or relative contraindications to beta-blockers. Thus, the apparent safety of intravenous beta-blockade during acute myocardial infarction has been confirmed only for carefully screened patients. Post hoc analysis of the major beta-blockade intervention trials suggests that the patients most likely to benefit from treatment are those at highest risk: specifically, individuals suffering from left ventricular dysfunction (28). Unfortunately, it is often clinically difficult to identify patients who will have adverse reactions to beta-blockers. Cardiac failure, hypotension, bradycardia or AV block follows initiation of beta-blockade in approximately 2 to 5% of carefully screened patients in the trials reported to date (4,9). These potential adverse side effects combined with the average 3 to 6 h biologic half-life of available beta-blockers frequently make clinicians wary of using such agents in patients with acute ischemia, especially if they have evidence of relative contraindications to beta-blockade (29).

As demonstrated in this group of patients with moderately compromised left ventricular function, esmolol at relatively low doses (50 to 150 μg/kg per min) induced a rapid decline of 10 to 15% in both heart rate and arterial systolic pressure. Further increases in the infusion rate rarely had additional negative chronotropic effect though systolic pressure continued to decrease in a dose-dependent fashion. It was frequently possible to adjust concurrently administered intravenous nitroglycerin to produce the desired degree of beta-blockade without unduly compromising arterial pressure. This degree of decline in heart rate and blood pressure with esmolol is comparable with that reported in studies of similar patients treated with other longer-acting intravenous beta-blockers as well as in prior studies with esmolol in patients who were undergoing preoperative tracheal intubation or who developed supraventricular tachycardia after cardiac surgery (21–23, 30–33).

Of particular importance in these patients with compromised cardiac function was the absence of any significant change in left ventricular filling pressure during the esmolol infusion, which lasted for up to 48 h (Fig. 3). Even those individuals who required a dose reduction or termination of the infusion because of hypotension or low cardiac output had no appreciable rise in pulmonary capillary wedge pressure. This finding is similar to results with other beta-blockers in patients with acute ischemia and normal or abnormal ventricular function (31,34,35). Although there was a trend toward a reduction in cardiac index during the esmolol infusion in this study, it failed to achieve statistical significance. Comparable effects on cardiac output and pulmonary capillary wedge pressure were obtained with esmolol by Iskandrian et al. (36) in their study of 10 patients with a mean radionuclide-confirmed baseline left ventricular ejection fraction of 27 ± 2% (range 20 to 36%).

Duration of action. The present study confirms previous observations of esmolol's short duration of action in animals, normal volunteers and patients with supraventricular tachycardia, perioperative hypertension or tachyarrhythmias or acute ischemia. Because intercurrent drug administration as well as an evolving clinical course over the 24 to 48 h infusion period may have altered the hemodynamic status of individual patients, pre- and postesmolol hemodynamic variables were occasionally slightly different. However, each patient had clear findings of rapid termination of drug effect by evidence of restoration toward baseline hemodynamics within 15 to 30 min of esmolol termination. Erythrocyte esterases are responsible for the hydrolysis of esmolol; thus, neither renal nor hepatic flow or function is central to metabolism of the drug (37). Consequently even in these patients with compromised left ventricular function, an extremely short biologic half-life was maintained.

Clinical implications. As shown in this series of patients, esmolol can safely lower heart rate, arterial pressure and rate-pressure product in patients with acute myocardial ischemia or infarction and moderate left ventricular dysfunction. This beneficial hemodynamic effect is titratable and appears to be achievable at a dose range of 50 to 200 μg/kg per min without clinically significant changes in pulmonary capillary wedge pressure, cardiac index or AV conduction. Although similar hemodynamic effects have been demonstrated with longer-acting beta-blockers in patients with a comparable degree of ischemic heart disease, esmolol's ultrashort duration of action permits greater flexibility in adapting the desired degree of beta-blockade to the patient's evolving clinical status. The duration of undesirable re-

sponses to beta-blockade during and after termination of esmolol infusion is minimized by the drug's short biologic half-life, and clinical stability is easily restored with modification of the dose (Fig. 4). Furthermore, the co-administration of nitroglycerin was safely accomplished in nine patients. Five patients did not require any adjustment in the infusion rate of nitroglycerin, whereas four required downward titration of the nitroglycerin infusion rate to maintain systolic arterial pressure >90 mm Hg.

Combination of antiischemic therapies. Thrombolytic therapy or percutaneous transluminal coronary angioplasty, or both, may limit infarct size and reduce morbidity and mortality in patients treated within hours of acute coronary occlusion. Zalewski et al. (38) demonstrated both a delayed development and a decreased magnitude of ST segment elevation during balloon dilation when patients undergoing coronary angioplasty were simultaneously treated with intracoronary propranolol. Several studies in dogs (39,40) suggest that there is enhanced salvage of ischemic myocardium or earlier functional recovery of infarcted tissue when beta-blockade is combined with early reperfusion. Intravenous administration of beta-blockers soon after the onset of infarction in humans may have an additive salutary effect on myocardial infarct size when combined with thrombolysis or coronary angioplasty (41). In addition, early treatment with beta-blockers may favorably alter myocardial oxygen demands, thereby slowing the progress of necrosis through the myocardium and widening the therapeutic window for reperfusion. These concepts are currently being explored in large randomized clinical trials (42) with longer-acting beta-blockers.

Because the sympathetic tone of patients in the first few hours after myocardial infarction may be different from that reported in the patients in this study, an important question for further study is the role of esmolol in the earliest stages of acute infarction. Use of an easily titratable, ultrashort-acting, cardioselective beta-blocker such as esmolol in situations where there are relative contraindications to beta-blockade would broaden the clinical applicability of this important adjunctive pharmacotherapeutic option in the current era of reperfusion therapy for myocardial infarction.

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